

DEDICATION

To my parents,

My wife,

My children,

My teachers,

and friends

For giving me never-ends gifts of encouragement, love and patience

ACKNOWLEDGMENT

I would like to express my sincere gratitude to

Dr. Mohamed Mohamed Omer and Dr. Mohammed Elfadil

who has given me great advice and help in the whole process of my thesis for his fruitful day to day supervision, guidance, endless help and encouragement that built confidence in my work for his valuable and continuous help, his patience through all the years that made this work possible for giving this opportunity of study, and for endless encouragement and unlimited support.

My thanks extend also to colleagues who contribute in the sample collections.

I would like to thank everyone who assisted by one way or another to bring this study to the light.

ABSTRACT

Bone scan is the accepted initial imaging modality for skeletal metastases. Some patients use chemotherapy in the initial stages before and after surgery for breast cancer patients according to the international protocol, this study aimed to evaluate the time elapsed between bone scan and chemotherapy dose that effected on renal function by GFR measurement. It is a retrospective study designed and conducted in the Nuclear Medicine Department, king Abdulla medical city (KSA) which included 150 female breast cancer patients with age ranged between 25-75 years, weighing 40-120 kg were used in the study. All patients were diagnosed as breast cancer according to the histopathology report and were received all chemotherapy treatment accepted group control.

The results of this study revealed that the most common drugs used for adjuvant and nan adjuvant(cisplatin combination) chemotherapy effect on GFR and this significant correlation increased significantly when comparing the value of GFR after chemotherapy treatment to the values of maximum bone counts to be -.007 and all count decreasing after treatment in all groups and there are a direct linear relationship between the acquired counts and the elapse time after chemotherapy, the coefficient of this relationship indicates that the researcher applied the specific threshold segmentation in order to increase the image quality by decreasing the values of the counts per background pixel and increased the value of counts per bone region pixel and increasing the ratio between the background counts to the bone region counts per pixel, the result showed a strong significant correlation of 0.733 between the applied threshold significant and the ratio of bone counts to the background counts the researcher set a values of

recommended threshold segmentation which should be applied for bone scan image to the patients treated with chemotherapy, these set of segmentation values was depends on the time intervals between the bone scan and the chemotherapy treatments in order to increase the image quality to be quite diagnosable, the threshold segmentation should be increased by a factors of 54.4%, 130%, 218.2% and 278.2% form the threshold segmentation of the normal control groups of patients for bone scan after 4,3,2 and 1 weeks from chemotherapy treatments respectively. This study concluded that The suitable time of bone scan post chemotherapy 4 week.

ملخص البحث

فحص العظام هو طريقة التصوير الأولية المقبولة لتشخيص الهيكل العظمي يستخدم بعض المرضى العلاج الكيميائي في المراحل الأولية قبل وبعد الجراحة لمرضى سرطان الثدي وفقا للبروتوكول الدولي، تهدف هذه الدراسة إلى تقييم الوقت المنقضى بين فحص العظام و جرعة العلاج الكيميائي التي تؤثر على وظيفة الكلي عن طريق قيا س مستوي التصفية الدموي وهي دراسة استعادية تم تصميمها وإجرائها في قسم الطب النووي بمدينة الملك عبد الله الطبية والتي تضمنت 150 مريضا سرطان الثدي تتراوح أعمار هن بين 25-75 سنة، وبلغ وزنهن 40-120 كغم في الدراسة. تم تشخيص جميع المرضى على أنها سرطان الثدي وفقا لتقرير الأنسجة المرضية، وتم تلقي جميع المرضي والعلاج الكيميائي ماعدا مجموة التحكم في الدراسة. اظهرت نتائج هذه الدراسة ان الأدوية الاكثر شيوعا المستخدمة في العلاج الكيميائي مثل تركيبات (تركيبة سيسبلاتين) للعلاج الكيميائي تاثير مباشر على مستى التصفية الدمويه بواسطة الكلى وازداد هذا الارتباط معنويا عند مقارنة قيمة التصفيه الدموية بعد العلاج الكيميائي لقيم التعداد العظمى الأقصى لتكون - .0.007 وكل العد يتناقص بعد العلاج في جميع المجموعات، وهناك علاقة خطية مباشرة بين التراكيز المكتسبة والوقت الفاصل بعد العلاج الكيميائي، ويشير معامل هذه العلاقة إلى أن الباحث طبق تجزئة العتبة البرمجية المحددة من أجل زيادة جودة الصورة من خلال خفض قيم التعداد لكل بكسل في الخلفية وزيادة قيمة التعداد لكل بكسل في منطقة العظام وزيادة النسبة بين عدد الخلفية إلى التعداد منطقة العظام لكل بكسل، وأظهرت نتيجة وجود علاقة قوية من 0.733 بين الاثر المعالج لقيمة العتبة المطبقة بنسبة عالية ونسبة التعداد للعظام إلى نسبة الخلفية وضع الباحثة قيم تجزئة العتبة الموصى بها والتي يجب تطبيقها على صورة المسح العظمي للمرضى المعالجين بالعلاج الكيميائي، وقد اعتمدة هذه المجموعة من قيم التجزئة على الفترات الزمنية بين فحص العظام والعلاج الكيميائي من أجل زيادة جودة الصورة لتكون قابلة للتشخيص تماما، وينبغي زيادة تجزئة عتبة على حسب المجموعات كلاتي 54.4%، 130٪، 218.2٪ و 278.2٪ تشكل هذه العوامل لتجزئة العتبة لمرضى بسرطان الثدي لفحص العظام بعد 4،3،2 و 1 أسابيع من العلاج الكيميائي على التوالي. وخلصت هذه الدراسة إلى أن

Table of contents

الوقت المناسب لمسح العظام الذين تم معالجتهم بالعلاج الكيميائي بعد 4 أسابيع من العلاج

لتعطى صوره وإضحة يتم تشخيصها بشكل مثالى.

| Subject | Subject | Page number |
|---------|--------------------|-------------|
| Number | | |
| | الإية | I |
| | Dedication | II |
| | Acknowledgement | III |
| | Abstract (English) | IV |
| | Abstract (Arabic) | VIII |

| | List of Tables | XI |
|---------------------------------|--|-----|
| | List of Figures | XII |
| | List of Abbreviations | XIV |
| | Table of contents | XV |
| | CHAPTER ONE(Introduction) | |
| 1.1 | Introduction | 1 |
| 1.2 | Problem of the study | 4 |
| 1.3 | Objectives of the study | 4 |
| 1.3.1 | General objective | 4 |
| 1.3.2 | Specific objective | 4 |
| 1.4 | Significance of the study | 5 |
| 1.5 | Overview of the study | 5 |
| CHAPTER TWO (Literature review) | | |
| 2.1 | Anatomy of the bone | 6 |
| 2.2 | Physiology of the Bone | 9 |
| 2.3 | Physiology of the Bone | 9 |
| 2.4 | Function of bones | 11 |
| 2.5 | Blood disorders caused by chemotherapy | 11 |
| 2.6 | Bone pathology | 12 |
| 2.6.1 | Etiology of bone disease | 12 |
| 2.6.2 | Ki Kidney Malfunction | 12 |
| 2.6.3 | Overactive Parathyroid glands | 12 |
| 2.6.4 | Poor Bone Metabolism | 13 |
| 2.6.5 | Decrease in Sex Hormones | 13 |
| 2.6.6 | Genetics | 13 |
| 2.6.7 | Osteomyelitis | 13 |
| 2.6.8 | Osteosarcoma | 13 |
| 2.7 | Bone metastasis | 14 |
| 2.7.1 | Type of bone metastases | 14 |
| 2.7.2 | bone as a preferred site of metastasis | 17 |

| 2.7.3 | control of normal bone remodeling | 18 |
|---------|---|----|
| 2.7.4 | osteocytes metastasis from breast cancer the vicious circle | 18 |
| 2.8 | Type of bone metastasis treatment | 20 |
| 2.8.1 | Hormone therapy | 20 |
| 2.8.2 | Targeted therapy | 20 |
| 2.8.3 | Immunotherapy | 21 |
| 2.8.4 | Radiopharmaceuticals | 21 |
| 2.8.5 | Other drugs for bone metastases | 22 |
| 2.8.5.1 | Bisphosphonates | 22 |
| 2.8.5.2 | Medication-related osteonecrosis of the jaw | 22 |
| 2.8.5.3 | Denosumab | 23 |
| 2.8.5.4 | Local treatments for bone metastases | 23 |
| 2.8.6 | External radiation therapy | 24 |
| 2.8.7 | Ablation techniques | 24 |
| 2.8.8 | Radiofrequency (RFA) | 24 |
| 2.8.9 | Bone cement | 25 |
| 2.8.10 | Surgery | 25 |
| 2.8.11 | Clinical trials | 25 |
| 2.9 | The breast anatomy | 26 |
| 2.10 | Chemotherapy for breast cancer | 27 |
| 2.10.1 | After surgery (adjuvant chemotherapy): | 27 |
| 2.10.2 | Before surgery (neoadjuvant chemotherapy) | 27 |
| 2.10.3 | For advanced breast cancer | 28 |
| 2.10.4 | Cisplatin | 28 |
| 2.10.5 | Cisplatin combinations in breast cancer | 29 |
| 2.10.6 | Cisplatin Cellular Mechanisms | 30 |
| 2.11 | Anatomy and physiology of the kidneys | 31 |
| 2.11.1 | Structure | 32 |
| 2.11.2 | Function | 33 |
| 2.11.3 | Evaluation of kidney function in cancer patients | 34 |

| 2.11.4 | GFR calculation | 36 | |
|--------|---|----|--|
| 2.11.5 | eGFR And Chemotherapy | 37 | |
| 2.12 | Gamma camera | 37 | |
| 2.12.1 | Gamma camera quality control | 38 | |
| 2.12.2 | Acquisition of bone scintigrams | 39 | |
| 2.13 | MatLab | 39 | |
| 2.14 | Image quality in nuclear medicine | 41 | |
| 2.14.1 | The intrinsic resolution | 42 | |
| 2.14.2 | Image analysis and processing in nuclear medicine | 42 | |
| 2.14.3 | Image processing techniques - MatLab | 43 | |
| 2.14.4 | Contrast enhancement | 43 | |
| 2.15 | previous study. | 44 | |
| | CHAPTER THREE(Materials and Methods) |) | |
| 3.1 | Material | 53 | |
| 3.1.1 | Material | 53 | |
| 3.1.2 | Equipment used | 54 | |
| 3.2 | Method | 54 | |
| 3.2.1 | Study protocols methods (techniques) | 54 | |
| 3.2.2 | preparation of 99mTc-MDP injection | 54 | |
| 3.2.3 | patient preparations | 55 | |
| 3.2.4 | Patient positioning | 55 | |
| 3.2.5 | Mode of administration of 99mTc-MDP | 55 | |
| 3.2.6 | Imaging Procedure | 55 | |
| 3.2.7 | GFR calculation | 56 | |
| 3.2.8 | Method of data analysis | 57 | |
| 3.3 | Ethical Consideration | 57 | |
| | CHAPTER FOUR | | |
| 4.1 | Results | 58 | |
| | CHAPTER FIVE | | |
| | | | |

| 5.1 | Discussion | 90 |
|------------|-----------------|-----|
| 5.2 | Conclusion | 97 |
| 5.3 | Recommendations | 98 |
| References | References | 100 |
| Appendices | Appendices | |

List of Tables

| Table number | Table content | Page number |
|--------------|--|-------------|
| Table 2-1 | Normal rang in depend calculate in this study | 36 |
| Table 4-1 | Statestic for all Patients groups (G2,G3G,4,G5): | 74 |
| Table 4-2 | statestic correlation of GFR threshold and bone ration for all Patients groups (G2,G3G,4,G5) | 74 |
| Table 4-3 | That shows anova sig for all group between GFR and threshold Segmentation | 75 |
| Table 4-4 | that shows coefficients for all group between GFR and threshold Segmentation and ratio of bone value | 75 |
| Table 4-5 | That shows correlation for all group between GFR after chemotherapy and threshold Segmentation and ratio of bone value | 75 |
| Table 4-6 | that shows statistics of group G1 | 79 |
| Table 4-7 | That shows correlation for G1 group between GFR after chemotherapy, GFR base line and Ratio of Bone Per Pix/BgPerPix and ratio of bone value | 80 |
| Table 4-8 | that shows anova sig for G1 group between GFR after chemotherapy, threshold Segmentation and Ratio of Bone Per Pix/BgPerPix | 80 |
| Table 4-9 | that shows coefficients for G1 group between GFR and threshold Segmentation and ratio of bone value (Ratio of Bone Per Pix/BgPerPix) | 81 |
| Table 4-10 | That shows statistics of group G2 | 81 |
| Table 4-11 | that shows correlation for G2 group between GFR after chemotherapy, GFR base line and Ratio of Bone Per Pix/BgPerPix and ratio of bone value | 82 |
| Table 4-12 | that shows anova sig for G2 group between GFR after chemotherapy, threshold Segmentation and Ratio of Bone Per Pix/BgPerPix | 82 |
| Table 4-13 | that shows coefficients for G2 group between GFR and threshold Segmentation and ratio of bone value (Ratio of Bone Per Pix/BgPerPix) | 83 |
| Table 4-14 | That shows statistics of group G3 | 83 |
| Table 4-15 | That shows correlation for G3 group between GFR after chemotherapy, GFR base line and Ratio of Bone Per Pix/BgPerPix and ratio of bone value | 84 |

| Table 4-16 | that shows anova sig for G3 group between GFR after chemotherapy, threshold Segmentation and Ratio of Bone Per Pix/BgPerPix | 84 |
|------------|--|----|
| Table 4-17 | that shows coefficients for G3 group between GFR and threshold Segmentation and ratio of bone value (Ratio of Bone Per Pix/BgPerPix) | 85 |
| Table 4-18 | that shows statistics of group G4 | 85 |
| Table 4-19 | that shows correlation for G4 group between GFR after chemotherapy, GFR base line and Ratio of Bone Per Pix/BgPerPix and ratio of bone value | 86 |
| Table 4-20 | that shows anova sig for G4 group between GFR after chemotherapy, threshold Segmentation and Ratio of Bone Per Pix/BgPerPix | 86 |
| Table 4-21 | that shows coefficients for G4 group between GFR and threshold Segmentation and ratio of bone value (Ratio of Bone Per Pix/BgPerPix) | 87 |
| Table 4-22 | that shows statistics of group G5 | 87 |
| Table 4-23 | that shows correlation for G5 group between GFR after chemotherapy, GFR base line and Ratio of Bone Per Pix/BgPerPix and ratio of bone value | 88 |
| Table 4-24 | that shows anova sig for G5 group between GFR after chemotherapy, threshold Segmentation and Ratio of Bone Per Pix/BgPerPix | 88 |
| Table 4-25 | that shows coefficients for G5 group between GFR and threshold Segmentation and ratio of bone value (Ratio of Bone Per Pix/BgPerPix) | 89 |

List of Figures

| No of figure | Figure repression | Page number |
|--------------|---|-------------|
| Figure 1-1 | Whole-body bone scintigraphy of a patient showing multiple hot spots | 3 |
| Figure 2-1 | Showing the skeletal system. | 8 |
| Figure 2-2 | Femoral blood supply. The principal nutrient artery and its main medullary branches are shown in this angiograph of a rabbit femur. | 11 |
| Figure 2-3 | Osteoclasts and Osteoblasts in Normal Bone and Bone Metastasis. | 16 |
| Figure 2-4 | Regulation of Bone Resorption (Panel A) and Bone Formation (Panel B). | 17 |
| Figure 2-5 | Receptor Activator of Nuclear Factor B Ligand (RANKL) and Osteoclast Formation. | 20 |
| Figure2-6 | location of the kidneys | 32 |
| Figure 2-7 | shows cross-section of kidney | 33 |
| Figure 2-8 | System of image acquisition using e.cam single-photo emission computed tomography system | 37 |
| Figure4-1 | age frequency of control patient | 58 |
| Figure4-2 | height frequency of control group patient | 59 |
| Figure4-3 | weight frequency of all patient | 59 |
| Figure 4-4 | scatter plot shows the correlation of GFR after chemotherapy and ratio of bone per/background per pixel For controlling group | 60 |
| Figure 4-5 | . scatter plot shows the correlation of GFR after chemotherapy and threshold segmentation For controlling group | 61 |
| Figure 4-6 | scatter plot shows the correlation of GFR after chemotherapy and ratio of bone per/background per pixel For Group G1 | 62 |
| Figure 4-7 | scatter plot shows the correlation of GFR after chemotherapy and threshold segmentation For group G2 | 63 |
| Figure 4-8 | age frequency of group G2 patient | 63 |
| Figure 4-9 | height frequency of group G2 patient | 64 |
| Figure 4-10 | weight frequency of group G2 patient | 64 |
| Figure 4-11 | scatter plot shows the correlation of GFR after chemotherapy and ratio of bone per/background per pixel For G3 group | 65 |
| Figure 4-12 | scatter plot shows the correlation of GFR after chemotherapy and threshold segmentation For group G3 | 66 |
| Figure 4-13 | age frequency of group G3 patient | 67 |

| Figure 4-14 | height frequency of group G3patient | 67 |
|-------------|---|----|
| Figure 4-15 | weight frequency of group G3patient | 68 |
| Figure 4-16 | scatter plot shows the correlation of GFR after chemotherapy and ratio of bone per/background per pixel For G4 group | 68 |
| Figure 4-17 | scatter plot shows the correlation of GFR after chemotherapy and threshold segmentation For group G4 | 69 |
| Figure 4-18 | age frequency of group G4 patient | 69 |
| Figure 4-19 | height frequency of group G4 patient | 70 |
| Figure 4-20 | weight frequency of group G4 patient | 70 |
| Figure 4-21 | scatter plot shows the correlation of GFR after chemotherapy and ratio of bone per/background per pixel For G5 group | 71 |
| Figure 4-22 | scatter plot shows the correlation of GFR after chemotherapy and threshold segmentation For group G5 | 72 |
| Figure 4-23 | age frequency of group G5 patient | 72 |
| Figure 4-24 | height frequency of group G5 patient | 73 |
| Figure 4-25 | weight frequency of group G5 patient | 73 |
| Figure 4-26 | shows' the scatter blot and linier regration between bone ratio value and GFR after chemotherapy in all groups (G2G3G4G5) | 76 |
| Figure 4-27 | shows' the scatter blot and linier R2 between threshold value and GFR after chemotherapy in all groups (G2G3G4G5) | 77 |
| Figure 4-28 | age frequency of all Patients groups (G2,G3G,4,G5) | 78 |
| Figure 4-29 | height frequency of all Patients groups (G2,G3G,4,G5) | 78 |
| Figure 4-30 | weight frequency of all Patients groups (G2,G3G,4,G5) | 79 |

List of abbreviations

| CT | Computed tomography |
|---------|--|
| Tc-99m | methylene diphosphonate |
| MDP | |
| GFR | glomerular filtration rate |
| ECM | extracellular matrix |
| D 3 | dihydroxyvitamin |
| T3 | thyroxine |
| RANKL | Receptor Activator of Nuclear Factor B Ligand |
| CSFs | colony-stimulating factors |
| PTHR1 | parathyroid hormone bind the same receptor |
| E2 | Prostaglandin |
| ONJ | Osteonecrosis jaw |
| RFA | Radiofrequency ablation |
| PMMA | Polymethylmethacrylate (Acrylic) |
| DX | Oncotype drug |
| 5-FU | 5-fluorouracil |
| G-CSF | Granulocyte colony-stimulating factor |
| CTCb | CTCb |
| CRs | complete responses |
| DNA | deoxyribonucleic acid, is defined as a nucleic acid that |
| | contains the genetic code. |
| EPO | Erythropoietin |
| MDRD | The Modification of Diet in Renal Disease |
| CKD-EPI | Creatinine Equation (2009) to estimate GFR |

| IRMA | Renal Insufficiency and Anticancer Medications |
|--------|--|
| BIRMA | Belgian Renal Insufficiency and Anticancer Medications |
| eGFR | Estimated glomerular filtration rate |
| SPECT | Single Photon Emission Computed Tomography |
| PET | Positron Emission Tomography |
| MatLab | Matrix Laboratory |
| DICOM | Digital Imaging and Communications in Medicine, |
| SNR | signal-to-noise-ratio |
| MCI | Ml curi |
| EDTA | Ethylenediaminetetraacetic acid |
| USA | United States of America |